

**REMARKS**

Reconsideration is requested.

Claims 37-39, 42-51, 53-65 and 67-76 are pending. Claims 51, 54-65 and 67-72 have been withdrawn from consideration.

Claim 37 has been amended by specifying the molar ratio coupling agent/N-hydroxysuccinimide compounds being from 2 to 20. Claims 47, 75 and 76 have been amended, as suggested by the Examiner, to obviate the Section 112, second paragraph, rejection of claims 47, 75 and 76. Entry of the present Amendment is requested to at least reduce this issue for appeal. Entry of the present Amendment and withdrawal of the Section 112, second paragraph, rejection of claims 47, 75 and 76 are requested.

The Section 102 rejection of claims 37-39, 42-50 and 73-75 over Qiu (U.S. Patent Application Publication No. 2003/0143335) and "Admitted Prior Art for support, found in specification page 4, lines 6-20", is traversed. Reconsideration and withdrawal of the rejection are requested for the reasons of record as well as the following further remarks.

As previously explained in the remarks of the Amendment filed April 5, 2011, Qiu describes a method for modifying the surface of an article by depositing a polyelectrolytic tie layer onto the surface of said article. The example K (¶[0400] of the cited application) describes the deposition of a polyelectrolytic layer onto the surface of contact lenses, the layer being obtained by reaction between polyacrylic acid (PAA) and polyalkylamine hydrochloride (PAH), with ED and NHS. The method described in this

example comprises the steps of successively dipping lenses into solutions of PAA and PAH, and then dipping the lenses in a solution comprising EDC and NHS with a molar ratio EDC/sulfo-NHS of 0,36 (5mg of EDC and 12mg of sulfo-NHS in 10ml of water, corresponding to respectively 2mM of EDC and 5,5mM of sulfo-NHS and thus to a molar ratio EDC/sulfo-NHS equal to 2/5,5, which is approximately of 0.36).

The method according to amended claim 1 differs from the method of example K in Qiu by the implementation with a molar ratio coupling agent/N-hydroxysuccinimide compounds from 2 to 20.

Qiu does not disclose this specific ratio range.

Furthermore, the cited art fails to literally or inherently describe that the obtained polyelectrolytic film is crosslinked.

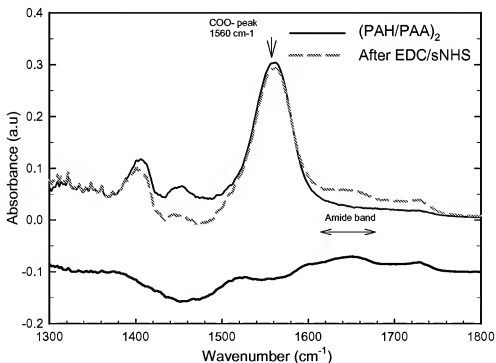
The applicants have previously demonstrated that a film according to example K of the cited art is not crosslinked. The Examiner has criticized the previously-submitted evidence as allegedly not "show[ing] the initial spectra before exposure to the NHS, in order to compare the two lines showing a different [sic] between the two and support the claim there is no crosslinking in the process described by Qui et al." See pages 3-4 of the Office Action dated June 23, 2011.

As mentioned above, the film of the cited art is a (PAH/PAA)<sub>2</sub> film deposited as described by the cited art (films built in water with PAH at pH 7.5 and PAA at pH 3.5; see example K, ¶[0400] and description of polyelectrolyte solutions page 20, ¶¶[0352]-[0353]). This film was then contacted with the EDC and sulfo-NHS solution with a molar ratio EDC/sulfo-NHS of 0.36. Film growth was followed by Fourier transform

spectroscopy (FTIR) in the attenuated total reflection (ATR) mode as described in the present patent application (see ¶ [0114]).

The graph of figure 1 below shows the spectrum of the  $(\text{PAH/PAA})_2$  film before contact with the EDC/sulfo-NHS solution (black line) and the spectrum of the same film after contact with the EDC/sulfo NHS solution (dash gray line). The difference between these two FTIR spectra (spectrum after contact with the EDC/sulfo-NHS minus that obtained for the film before contact with the EDC/sulfo-NHS solution) is plotted on the same graph (thick black line).

(Figure 1)



The above Figure 1 and Declaration of Ms. Catherine PICART filed April 15, 2011 therefore provide the showing alleged by the Examiner to be absent.

In the previously-submitted evidence and above Figure 1, the decrease of the  $\text{COO}^-$  peak of PAA is barely visible for the  $(\text{PAA/PAH})_2$ . Furthermore, the change in the amide band is very minor. A quantitative analysis of the  $\text{COO}^-$  peak of PAA (at  $1566\text{ cm}^{-1}$ ) showed a decrease of  $\text{COO}^-$  peak of PAA to be only of 6.5%. Based on the precision of FTIR experiments, a decrease of  $\text{COO}^-$  peak below 10% is not considered as significant. In other terms, cross-linking is not considered to occur if the change of the carboxylic group is below 10%.

The  $(\text{PAA/PAH})_2$  film of the cited art exhibited only a very minor change in structure and from the FTIR data one of ordinary skill would conclude that the films of the cited art have not been cross-linked, as confirmed by the Declaration of Ms. PICART. The Examiner will appreciate that Ms. PICART holds a degree in Materials Science from the Polytechnic Institute of Grenoble and a Masters degree in Biomedical Engineering from the University Joseph Fourier of Grenoble. Moreover, Ms. PICART has 12 years of work and research experience in the field of layer-by-layer films. Ms. PICART has concluded from the results of the above and previously-submitted Figure 1, in the Declaration of record, that "one of ordinary skill would conclude that the films of the reference [i.e., Qiu] have not been cross-linked." The Examiner has not provided any evidence to the contrary.

Figure 1A of the present application shows the spectrum of a  $(\text{PLL/HA})_8$  film obtained with the method according to the invention, before contact with the EDC/sulfo-NHS solution (black line) and the spectrum of the same film after contact with the EDC/sulfo NHS solution (dash gray line). The difference between these two FTIR

spectra (spectrum after contact with the EDC/sulfo-NHS minus that obtained for the film before contact with the EDC/sulfo-NHS solution) is plotted on the same graph (thick black line) (see figure 1A below).

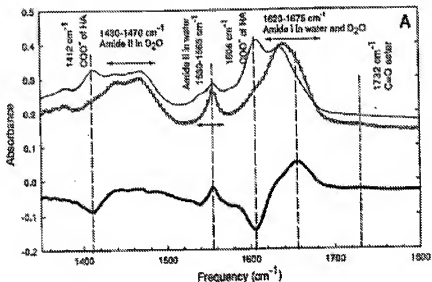


Figure 1A

The reaction between ammonium groups of PLL and carboxylate groups of HA in the presence of EDC/NHS was followed by FTIR-ATR. This cross-linking involves amine and carboxylic groups, which are converted to covalent amide bonds.

So, the applicants submit that the presence of a cross-linking reaction should be characterized by a significant decrease in the carboxylic peak and a significant increase in the amide band.

The applicants submit that one of ordinary skill will appreciate from the difference between the two spectra that, after contact with the EDC/NHS solution, the intensity of the peaks attributed to the carboxylic groups ( $1606$ ,  $1412\text{ cm}^{-1}$ ) significantly decreases

and correlatively the intensity of the amide bands increases ( $1620\text{-}1680\text{ cm}^{-1}$ ). This is a strong indication for the formation of amide bonds between PLL and HA at the expense of carboxylic groups. Quantitative analysis of the FTIR spectra before and after cross-linking confirmed that the decrease of the carboxylic peak was of 70%, which indicated that 70% of the carboxylic peaks have been converted to covalent amide bonds.

Consequently, according to figure 1A and the above-cited elements, the applicants believe that it clearly shows that the film obtained with the method according to the invention is cross-linked.

The cited art fails to teach each and every aspect of the claimed invention.

Withdrawal of the Section 102 rejection is requested.

The Section 103 rejection of claim 53 over Qiu and Lennon (U.S. Patent No. 5,721,361) is traversed. Reconsideration and withdrawal of the rejection are requested as the secondary reference fails to cure the deficiencies of the primary reference noted above. Claim 53 is dependent from claim 37 and is patentable over the cited primary reference for reasons similar to those noted above with regard to the Section 102 rejection.

Moreover, the applicants submit that the claims differ from the cited art in that the molar ratio coupling agent/N-hydroxysuccinimide compounds is from 2 to 20 and the cross-linking of the film.

By implementing a specific molar ratio coupling agent/N-hydroxysuccinimide compounds, the method according to claim 37 allows to obtain a cross-linked

polyelectrolyte multilayers film, which is not the case with the method of Qiu or Qiu and Lennon.

Furthermore, the applicants submit that as a consequence of the cross-linking provided by the claimed invention, the obtained films are stabilized with respect to aggressive media, such as solvents, extreme pH, ionic strengths fluctuations, enzymes and/or phagocytic cells, and particularly the films have an increased resistance against a certain medium and exchanges of this medium against another one (pH fluctuation, change of solvent, etc). This stability is demonstrated in the present specification (see ¶¶ [0017], [0131] and [0132] of the present application).

Qiu neither discloses nor suggests a method for preparing cross-linked polyelectrolyte multilayers films, including the use a coupling agent and N-hydroxysuccinimide compounds with a molar ratio of coupling agent/N-hydroxysuccinimide compounds from 2 to 20. The problem being solved by Qiu is not to prepare cross-linked polyelectrolyte multilayer films, but to provide a method of modifying the surface of a substrate with a polyelectrolytic film which allows active agents to adhere to the surface of the substrate.

Further, there is neither any description nor any suggestion in Qiu of a polyelectrolytic film having the above cited properties.

Lennon describes a method for preparing substituted polyazamacrocyles by reacting a diamine compound with a dicarboxylic acid or ester thereof.

Lennon neither describes nor suggests a method for preparing cross-linked polyelectrolyte multilayers films, including the use a coupling agent and N-

hydroxysuccinimide compounds with a molar ratio of coupling agent/N-hydroxysuccinimide compounds from 2 to 20.

Lennon neither describes nor suggests a crosslinked polyelectrolytic film comprising 5 to 60 layer pairs of cationic polyelectrolytes and anionic polyelectrolytes. Furthermore, Lennon neither teaches nor suggests a polyelectrolytic film having properties of the films of the present disclosure.

The claimed invention would not have been obvious in view of the cited art.

Withdrawal of the Section 103 rejection is requested.

The Section 103 rejection of claim 76 over Qiu and Rubner (U.S. Patent Application Publication No. 2003/0157260), is traversed. Reconsideration and withdrawal of the rejection are requested as the secondary reference fails to cure the deficiencies of the primary reference noted above. Claim 76 is dependent from claim 37 and is patentable over the cited primary reference for reasons similar to those noted above.

Rubner describes a method of coating a surface comprising sequentially depositing on the said surface alternating layers consisting of cationic and anionic polyelectrolytes.

Rubner neither describes nor suggests a method for preparing cross-linked polyelectrolyte multilayers films, including the use a coupling agent and N-hydroxysuccinimide compounds with a molar ratio of coupling agent/N-hydroxysuccinimide compounds from 2 to 20.



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Furthermore, Rubner neither teaches nor suggests a polyelectrolytic film having properties of the films of the present disclosure.

The claimed invention would not have been obvious in view of the cited combination of art. Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required in this regard.

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

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